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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,519	05/03/99	MIDOUX	P 410.015

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EXAMINER	
NGUYEN,D	
ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 12/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/297,519	Midoux
Examiner	**Group Art Unit**
Dave Nguyen	1633

☒ Responsive to communication(s) filed on Aug 30, 2000.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 20-44 is/are pending in the application.

Of the above, claim(s) 41-44 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 20-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 1 & 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Election/Restriction

Applicant's election without traverse of the Group I claims (claims 20-40) in the response filed on August 30, 2000 is acknowledged.

Claims 41-44 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to nonelected inventions.

Elected claims 20-40 are pending for examination.

Applicant is advised that the information regarding the cross-reference to the as-filed application as the national phase application under 35 U.S.C. 371 and its claim of priority to foreign applications under 35 U.S.C. 119 (a)-(d) should be stated the first paragraph of the specification.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

For applicant's convenience, the following guidelines are cited to illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to a "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross - Reference to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821 - 1.825).

Foreign documents, WO 92/13570, PCT written Opinion with respect to PCT/FR97/02022, FR 2.107.756, EP 0387775, EP 0388758, FR 2 719 316 submitted with the IDS of record have been considered only to the extent possible without an English Translation.

Sequence Rules

This application contains sequence disclosures (see page 20, and claim 33, for example) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-40, at best understood, are readable on a polymeric complex comprising of DNA and a polymeric conjugate which comprises an unspecified polymer formed from monomers having free NH3+ groups, wherein at least 10% of which are substituted by unspecified residues that must exhibit a biological function of being protonated in a weakly acid medium causing destabilization of cell membrane, said unspecified residues also carrying an unspecified functional group that must exhibit a biological function of not being active with recognition signal recognized by a cell membrane receptor, and wherein some of the free NH3+ are substituted by non-charged residues having at least one-OH which must exhibit a biological function of not being active with the recognition signal recognized by a cell membrane receptor, which in turn may be substituted by unspecified cellular recognition signals, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention.

The specification and the state of the prior art of record provide sufficient description of polymeric complexes comprising the polymer with the formula as set forth in claim 34, wherein R is a residue with an imidazole nucleus, or a compound having the formulae as set forth on pages 12 and 13 of the as-filed specification, said polymer further conjugated to gluconyl based non-charged residues.

With respect to claims readable on a genus of polymers formed from monomers having free NH3+ groups which must exhibit a biological function of being able to function as a conjugate to other disclosed functional groups, *e.g.,* nucleic acid molecules, residues comprising an imidazole nucleus and an NH3+, gluconyl based non-charged residues, and cellular recognition signals, and to function as a whole as a nucleic acid transfer vector, the specification only provides sufficient description of the polymer with the formula as set forth in claim 29 or 34.

With respect to claims readable on a genus of unspecified residues that must exhibit a biological function of being protonated in a weakly acid medium and causing destabilization of cell membrane, said unspecified residues also carrying an unspecified functional group that must exhibit a biological function of not being active with recognition signal recognized by a cell membrane receptor, the specification only provides sufficient description of a polylysine based polymeric complex conjugated to residues having an imidazole nucleus and an NH3+ functional group, and residues having the formulae as set forth on pages 12 and 13 of the as-filed specification

With respect to claims readable on a genus of non-charged residues having at least one-OH which must exhibit a biological function of not being active with the recognition signal recognized by a cell membrane receptor, which in turn may be substituted by unspecified cellular recognition signals, the specification only provides sufficient description of a polysine based polymeric complex conjugated to residues having an imidazole nucleus and an NH3+ functional group and to gluconyl based non-charged residues.

With respect to claims readable on a genus of cellular recognition signals, the specification only provides sufficient description of cellular recognition signals which are peptide based recognition signal

sequence, oligosaccharide based recognition signal or monosaccharide based recognition signal.

With respect to claims readable on a genus of certain fragments of anti-inflammatory peptides, the specification discloses no specific or "certain fragments" as claimed.

With respect to claims readable on a genus of "antagonists" of peptide hormones, the specification discloses no specific antagonists or a representative number of species of antagonists as claimed.

With respect to claims readable on a genus of "ribozymes" as therapeutic DNA, the specification discloses no specific ribozymes and/or a representative number of species of antagonists as claimed.

In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for making the polymer genus as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of polymeric conjugates and/or functional groups thereof that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention by disclosing polymeric complexes comprising the polymer with the formula as set forth in claim 34, wherein R is a residue with an imidazole nucleus, or a compound having the formulae as set forth on pages 12 and 13 of the as-filed specification, said polymer further conjugated to gluconyl based non-charged residues, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other polymeric conjugates having other residues with the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all polymeric conjugates and/or functional groups and/or therapeutic DNA thereof that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC,

1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed polymeric complexes that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

DNA/polymeric complexes comprising the polymer with the formula as set forth in claim 34, wherein R is a residue with an imidazole nucleus, or a compound having the formulae as set forth on pages 12 and 13 of the as-filed specification, said polymer further conjugated to gluconyl based non-charged residues, wherein the recognition signals are peptide based, oligosaccharide based, or monosaccharide based recognition signals, which complexes exhibit the biological functions as disclosed in the base claim 22.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all other polymeric delivery vectors including those that embrace therapeutic applications as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of polymeric complexes as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended, *e.g.* functions as a nucleic acid delivery vector that exhibits all of the biological functions as recited in the claimed invention.

Furthermore, it appears that the only intended use of the claimed polymeric complexes is for enhancing delivery of nucleic acid molecules into a target cell so as to generate a more effective transmembrane passage of nucleic acid molecules as compared to well-known unsubstituted polylysine/DNA complexes and other substituted polymeric vectors having agents which reduce the number of charges on the polymeric vector. However, the state of the art exemplified by Verma, Nature, Vol. 389, pages 239-242, 1997, indicates:

"The Achilles hell of gene therapy is gene delivery, and this the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. There are two categories of delivery vehicle ('vector'). The first comprises the non-viral vectors, ranging from direct injection of DNA to mixing the DNA with polylysine or cationic lipids that allow the gene to cross the cell membrane. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene" (page 239, column 3).

Given that transient gene expression remains a major obstacle of gene transfer methods of using polylysine based vectors, as stated in Verma, and given that the claimed invention, *e.g.,* claims 21 and 34, for example, encompasses therapeutic applications of the DNA/polymeric complexes, it is not apparent as to how one skilled in the art determines, without undue experimentation, which of the disclosed gene therapy vector of polymeric complexes are effective for use as intended therapeutic complexes. Furthermore, it is apparent that only intended use of claimed polymeric complexes comprising a target cell

recognition signal from the as-filed disclosure is to use the complexes for targeted *in vivo* delivery of nucleic acids to any target cell. However, major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the treatment in a treated subject (Anderson, Nature, Vol. 392, pp. 25-30, April 1998). More specifically, Anderson teaches that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph), that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types. Verma *et al.* further state that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

With respect to the use of therapeutic DNA as claimed in claim 34 or as encompassed the *in vivo* gene therapy method claims including antisense, ribozymes, triplex oligonucleotides to treat a tissue *in vivo* therapeutically, the application does not demonstrate a therapeutic effect in any subject using any of the disclosed DNA as claimed. More specific as to the state of the art of antisense therapy, Branch (TIBS 23, pp. 45-50, 1998) even in 19998, antisense and ribozyme therapy remains unpredictable (entire document).

There is no factual evidence from the as-filed application of any *in vivo* beneficial affect generated

from any targeted gene transfer vector as claimed. The specification does not provide sufficient guidance and/or factual evidence demonstrating a reasonable correlation between the disclosure and the subject matter being sought in the claims. Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without any undue experimentation, from *in vitro* use of polymeric complexes comprising polylysine conjugated with residues comprising an imidazole nucleus and an NH3+,.and gluconyl based non-charged residues to any and/or all other claimed polymer complexes that embrace therapeutic applications as contemplated by the application. Thus, the specification is further not enabling under 35 U.S.C. 112, first paragraph, for any and/or therapeutic nucleic acid constructs within the context of treatment of any disease in any subject, particularly on the basis of applicant's disclosure and the reasons stated in the art of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite because the claim is dependent on a canceled claim, claim 12, thereby rendering the claim incomplete, *e.g.,* see MPEP 608.01(n)(V).

Claims 22, 24, 25, 36 and claims dependent therefrom are indefinite in the recitation of the phrase "and optionally containing a molecule ....by substitution of some of the free NH3 of the monomer...or some of the non-charged residues....or on some of the residues causing.....or on some the residues causing a destabilization of cell membranes by substitution of the optional free NH3+" because the phrase appears to be Markush-type claims , but do not appear to use accepted Markush language (MPEP 2173.05(h)(a)). In addition, the phrase as a whole is vague and does not point out the intended scope of the placement of the recognition signal in the polymeric complex as claimed, particularly since the incorporation of the "or on" renders the claim unclear as to its metes and bounds of the

placement of the recognition signal. In addition, the phrase "are not active with the recognition signal" is indefinite because the word "active" is relative in meanings and does not point out the intended scope of the claims. It is not apparent as to how the "are not active" occurs physically between the claimed residue and the recognition signal.. The term "the recognition signal" also lacks an antecedent basis because it is well-known in the art that there are plurality of recognition signal peptides, for example, that bind to a cell membrane receptor. The phrase "the recognition signal required by a cell membrane receptor" is also indefinite because it is not apparent as to how the "required" identifies the intended scope of the "recognition signal".

Claim 29 is also indefinite in the recitation of "and optionally by a molecule having a recognition signal" because it is not apparent as to what is exactly meant by "and optionally by". It is not apparent as to is exactly the active step that links structurally the "optionally by". In addition, the "recognition signal" is indefinite because it is not apparent as to is exactly the metes and bounds of the term, nor is it apparent as to what is exactly the materials that are recognized by the "signals". In addition, the phrase "10 to 90% of R being free ...optionally substituted 0 to 50%" is vague and confusing because it is not apparent as to what is exactly the meaning of the "optionally substituted 0 to 50%", particularly since the phase appears to miss a preposition word and is not grammatically correct.

Claim 30 is indefinite in the recitation of "R" because the base claims 26 and 27 do not recite any R. However, the claim states that R is in the complex of claim 27.

Claim 31 is indefinite in the recitation of "wherein m is 2 to 7 -NH-CO-(CH2OH)m-R1 and is selected from the group" is grammatically incorrect and thus, it is not apparent as to what is exactly the intended scope of the claim.

In claim 33, step a), the phrase "certain of their fragments" are indefinite because the phrase is relative in meanings and does not identify as to what exactly constitutes the relative meaning of "certain".

In claim 33, step C), the "certain cells" is indefinite because the term is relative in meanings and does not identify as to what exactly constitute the relative meaning of "certain".

Claim 34 is indefinite because the claim attempts to recite nucleic acid as "protein", "enzymes", or disease names, particularly since a nucleic acid or genes are not *per se* proteins, enzymes, or disease names. The claim should be amended to clarify the language by indicating, for example, that "gene coding from luciferase" instead of "genes containing luciferase", that "gene encoding factor VIII and IX" instead of "genes with a therapeutic purpose

selected from the group consisting of hypercholesterolaemia, ...". In addition, the phrase "genes which code for ribozymes" is definite because a ribozyme is not a gene that codes for a mRNA but rather a synthetic nucleic acid molecule. In addition, the term "such as" is indefinite because the term does not define the intended scope of the claim.

Claim 35 is indefinite in the recitation of "the lysine units" because the term is not present in the base claim 22, and thus, the term lacks an antecedent basis.

Claim 36 is indefinite in the recitation of "the above-mentioned polymer" because the term is not present in any where above the recitation in the claim, and thus, the term lacks an antecedent basis. In addition, the "monomer units being at least 10% by residues causing" is grammatically incorrect, and thus rendering the claim vague and confusing. Appropriate correction is required.

Claim 39 is indefinite in the recitation of "...and/or..." because the recitation fails to clearly define as to what is exactly the intended scope of the claim. The claim is also indefinite in the recitation of "corresponding" because the term is relative in meanings and does not define the intended scope "the protein".

In claim 40, the phrase "carrying a recognition signal being a function of a target cell optionally bonded beforehand to the polymer conjugate" is indefinite because it is not apparent as to how the signal is structurally linked to a polymeric conjugate of claim 36. In addition, it is not apparent as to which of the polymeric conjugate of claim 36 is intended to be claimed in claim 40 in view of the recitation of "a polymeric conjugate of claim 36". In addition, it is not apparent as how the "signal being a function of a target cell" is exactly to be meant. What is exactly the function applicant intends to define as a functional limitation for the recited "signal"? In addition, the term "reagent" as recited numerously in the claim and defined by only functional limitations are indefinite because it is not apparent as to what is exactly the metes and bounds of the "reagents". In addition, the term "system" is also indefinite because it is not apparent as to what is exactly the material(s) that constitute the "system" having the recited function.

Claim 27 is objected because "he" on line is a misspelling of "the".

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

To the extent that the claims, as best understood given numerous indefinite recitations present in the claims, are readable on a DNA/polymer complexes comprising a polylysine conjugated to a residue with an imidazole nucleus, said polymer further conjugated to gluconyl based non-charged residues, wherein the recognition signals are peptide based, oligosaccharide based, or monosaccharide based recognition signals, which complexes exhibit the biological functions as disclosed in the base claim 22, and are readable on *in vitro* gene transfer methods of using the complexes, the following rejection is applicable.

Claims 21-40 are rejected under 35 U.S.C. 103 as being unpatentable over either FR-A-2719316 (D1, cited in the written opinion from PCT officers) or Midoux *et al.* (US Pat No. 5,733,762, 3/1998, wherein Erbacher and Roche-Degremont constitute as another inventive entity, entire document), taken with Wang *et al.* (D3, cited in the Written Opinion from PCT officers).

D1 and Midoux describe a complex between at least one negatively charged nucleic acid and at least one positively charged polymeric conjugate bonded by electrostatic interaction. The polymeric conjugate contains a polymer of monomeric units with free NH3+ groups. The free NH3+ are substituted, with a ratio of at least 10%, by gluconyl based non-charge residues and do not bind to any recognition signal recognized by a cell membrane receptor (entire documents).

The difference between D1 or Midoux and the subject matter of the present claimed invention is that the claimed invention is directed to histidine residues that are protonable in a weakly acidic medium and further comprise a functional group enabling them to be bound to the polymer while not being recognized by a cell membrane receptor. The objective of employing histidine residues or residues with an

imidazole nucleus conjugated to polylysine, for example, is to enhance the protection of transfectinng nucleic acid from lysosomal decomposition following endocytosis.

However, at the time the invention was made, D3 describes the fusion-mediating properties of polyhistidine relative to liposomes. The concept of fusion is caused by the polycationic nature of polyhistidine having an acid pH, and to the combination of the polycation with membrane phospholipids that induces phase separation in the dual lipid layer (D3, abstract). D3 also indicates that the fusion-mediating behavior associated with polyhistidine having a low pH is more effective than the one associated with Ca2+ or polylysine. More specifically, D3 indicates that a charge ratio of only 0.2 or less between the polyhistidine and the liposome enables effective fusion to be ensured, whereas it must exceed 0.7 with Ca2+ and be of around 1 with polylysine (see page 4414, column 2, last sentence to page 4415, column 1, line 13; table IV). In addition and most importantly, D3 suggests that if the interaction between the hydrophobic segments of viral envelope glycoproteins is an important step in the fusion process, the protonation of the histidine residues of the viral protein with an acidic pH would be an alternative fusion means (page 4115, last paragraph).

It would have been obvious for one of ordinary skill in the art to have incorporated histidine residues to any of the free NH3 groups of the polylysine in D1 in order to enhance the fusion and translocation of DNA complexed with polylysine. One of ordinary skill in the art would have been motivated to have incorporated histidine residues to any of the free NH3 groups of the polylysine in D1 because of the reasons set forth in the preceding paragraphs.

To the extent that the claims are readable on specific substitution ratios, and further optional incorporation of cell-recognition peptides, it would have been obvious to one of ordinary skill in the art as a matter of design choice to employ any ratio and/or well known cell recognition peptides in the polymeric complexes of D1 taken with D3, particularly since such teachings are also disclosed in D1 (claims 1 and 4) and in Midoux *et al.*

To the extent that the claim are readable on residues belonging to the family of compounds that comprise an imidazole ring, having residues that are alkylimidazoles, the claims are directed to minor

modification and/or obvious variants of the polymeric complexes, and one of ordinary skill in the art would have been motivated as a matter of design choice to employ these well-known compounds as obvious variants of histidines, particularly since D1 teaches that the polymer includes a grouping of formula (I) and (II) (see D1, claims 6 and 8). Likewise, the selection of recognition signals, the selection of nucleic acids and the selection of the defining parameters of the polymer, *e.g.,* the substitution ration of the free NH3+ of the lysine units, the selection of the molecular weight of the nuclei acid and the average number of base pairs of the nucleic acid per monomeric unit molecule, are minor modification or options that a person of ordinary skill in the art would have been motivated to have as a matter of design choice, depending on each particular case (see D1, claims 11-13; and Midoux *et al.,* column 3-16). Thus, in the absence of unexpected results, the claims are obvious variants of one another.

Thus, the claimed invention as a whole was *prima facie* obvious.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-15 of U.S. Patent No. 5,733,762, 3/1998, claims 9-15, and further in view of D3. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are readable on

a complex between at least one negatively charged nucleic acid and at least one positively charged

polymeric conjugate bonded by electrostatic interaction. The polymeric conjugate contains a polymer of monomeric units with free NH3+ groups. The free NH3+ are substituted, with a ratio of at least 10%, by gluconyl based non-charge residues and do not bind to any recognition signal recognized by a cell membrane receptor.

The difference between Midoux and the subject matter of the present claimed invention is that the claimed invention is directed to histidine residues that are protonable in a weakly acidic medium and further comprise a functional group enabling them to be bound to the polymer while not being recognized by a cell membrane receptor. The objective of employing histidine residues or residues with an imidazole nucleus conjugated to polylysine, for example, is to enhance the protection of transfectinng nucleic acid from lysosomal decomposition following endocytosis.

However, at the time the invention was made, D3 describes the fusion-mediating properties of polyhistidine relative to liposomes. The concept of fusion is caused by the polycationic nature of polyhistidine having an acid pH, and to the combination of the polycation with membrane phospholipids that induces phase separation in the dual lipid layer (D3, abstract). D3 also indicates that the fusion-mediating behavior associated with polyhistidine having a low pH is more effective than the one associated with Ca2+ or polylysine. More specifically, D3 indicates that a charge ratio of only 0.2 or less between the polyhistidine and the liposome enables effective fusion to be ensured, whereas it must exceed 0.7 with Ca2+ and be of around 1 with polylysine (see page 4414, column 2, last sentence to page 4415, column 1, line 13; table IV). In addition and most importantly, D3 suggests that if the interaction between the hydrophobic segments of viral envelope glycoproteins is an important step in the fusion process, the protonation of the histidine residues of the viral protein with an acidic pH would be an alternative fusion means (page 4115, last paragraph).

It would have been obvious to one of ordinary skill in the art to have incorporated histidine residues to any of the free NH3 groups of the polylysine in D1 in order to enhance the fusion and translocation of DNA complexed with polylysine. One of ordinary skill in the art would have been motivated to have incorporated histidine residues to any of the free NH3 groups of the polylysine in D1 because of the reasons

set forth in the preceding paragraphs. Thus, the subject mater as claimed in this instant application, wherein histidine residues are incorporated to NH3+ groups of the polylysine polymer, is obvious variants of the subject matter as recited in claims 9-15 of the '762 patent.

To the extent that the claims are readable on specific substitution ratios, and further optional incorporation of cell-recognition peptides, it would have been obvious to one of ordinary skill in the art as a matter of design choice to employ any ratio and/or well known cell recognition peptides in the polymeric complexes of Midoux taken with D3, particularly since such teachings are also disclosed in the claims of Midoux (claim 9).

To the extent that the claim are readable on recognition signals, the selection of nucleic acids and the selection of the defining parameters of the polymer, *e.g.,* the substitution ration of the free NH3+ of the lysine units, the selection of the molecular weight of the nuclei acid and the average number of base pairs of the nucleic acid per monomeric unit molecule, are minor modification or options that a person of ordinary skill in the art would have been motivated to have as a matter of design choice, depending on each particular case (see claims 9-15). Thus, in the absence of unexpected results, the claims are obvious variants of one another.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 308-0009**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Patent Examiner
Art Unit: 1633

Application No.: 09/297,519

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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